American Journal of Pharmacy

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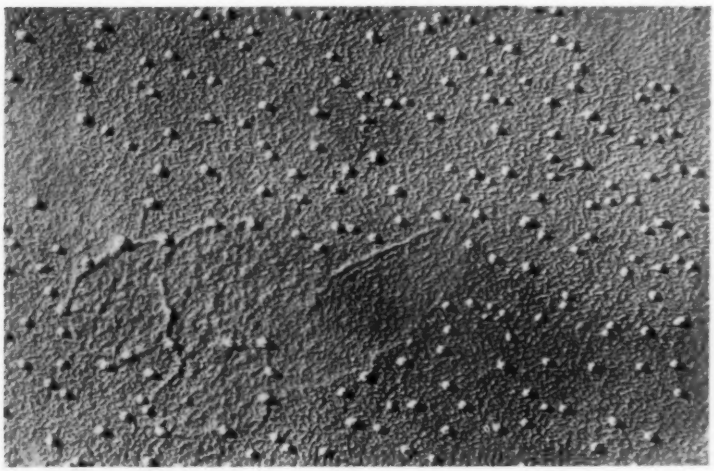

VIRUS OF INFECTIOUS HEPATITIS

Since 1825 *August 1961*

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SOME DRUM BEATING ABOUT THE PHARMACIST WHO PLAYED CHIEF

The day he got his store, he thought, "Now I'm my own boss." And he was.

He began by directing an aggressive buying operation (he did the buying). When the "bargains" arrived, he grunted orders to his warehouseman (himself). Then he cracked the whip over his billing clerk (also himself) and made his accountant (same man) work overtime when his capital got tied up in stock.

It dawned on him one day that being chief isn't much fun when you have to play Indian, too.

Moral

Lilly

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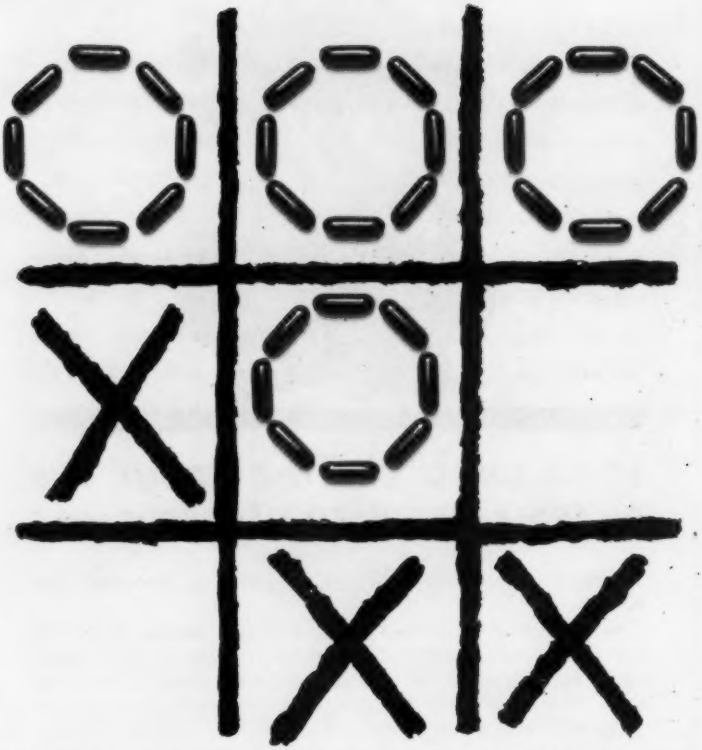

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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Our Cover, Virus of Infectious Hepatitis, is the first photograph ever taken of infectious hepatitis virus and was photographed by Dr. Alton R. Taylor of Parke, Davis & Company.

E D I T O R I A L

THE PROBLEM OF PHYSICIANS' SAMPLES

THAT there have been a number of serious abuses in the distribution and use of physicians' samples cannot be debated and it is equally true that the Food and Drug Administration could hardly postpone taking some action on this matter in view of some of the serious abuses which have been brought to light. Unfortunately, in attempting to correct abuses, the Food and Drug Administration seems to have gone a bit too far and to have taken a position which is, in our opinion, somewhat untenable in that it imposes a barrier between physician and pharmacist for which no logical and fundamental reasons exist.

The worst abuse which the government is now seeking to correct is the repackaging of physicians' samples by commercial enterprises. This is, without question, illegal and dangerous, and a hazard to both the professions and the public health. Those pharmacists who have been guilty of buying such repackaged drugs are themselves guilty of professional and ethical misconduct and no-one can argue against the position on this which the FDA has taken. The claim that physicians' samples often fall into lay hands is also equally true, and the several means whereby this was accomplished were both with and without the knowledge and consent of the individual physician. Often, we feel they were discarded in the wastebasket only to be retrieved by some fairly well informed layman who then proceeded to dose himself or his friends. Some few nurses have been notorious in their pursuit of the practice of medicine made possible by more or less judicious use of physicians' samples which they easily diverted from a physician's desk to their own handbag. Against all of these evils, we cannot but side with the Food and Drug Administration that public health and welfare demanded remedial action.

The one area in which we are forced to disagree is the position taken that physicians may not give a pharmacist a sample which they

have received for the express purpose of filling a *bona fide* prescription calling for that drug. In such an instance, the drug is at all times properly labeled with the name of the drug, its identity is never in question, a pharmacist is reasonably well prepared to judge its condition and quality, and at no time does it pass through lay hands until it arrives there through the medium of a prescription. In taking the position that the pharmacist is not privileged to use a physician's sample to fill a prescription, the FDA does not seem on sound ground since there seems to be little or no hazard to public health involved. There can, of course, be no intermediary such as exists in the commercial exploitation of physicians' samples since this indeed does interject lay people and breaks the chain of professional supervision.

Frequently, there are excellent reasons why a physician may wish to give a pharmacist a supply of some drug which he has received as a professional sample. He may, for example, only want his patient to take this drug in the form of a prescription medication rather than hand him the medication himself. Many physicians are loath to dispense drugs even though they are supplied with a free sample since to supply one patient at one time with medication and not to do this consistently causes some questions to arise and it does make of the physician a dispenser which, with those who are strictly ethical, is frowned upon. In other instances, the physician may wish to give some financial help to a patient who is impoverished and who cannot afford medication. A physician's sample supplied the pharmacist for this purpose is a convenient way to approach this problem, often making it unnecessary to tell the patient that he is the partial recipient of charity.

It is difficult, if not impossible, to draw the line between a professional sample sent the pharmacist and a professional sample sent the physician. Both are one and the same thing and both can be used legally only one way, namely, to provide medication for the patient under professional supervision and control.

While we strongly endorse the FDA position in bringing about controls in this area of drug distribution, it is our feeling that they have gone too far on this one point. We sincerely hope that further study and reflection will lead to an easing of this restraint since, insofar as pharmacists are concerned, this is a matter of principle wherein their professional rights are being abrogated without reason.

L. F. Tice

ATTENUATED LIVE MEASLES VACCINE

By Louis Gershenfeld *

MEASLES was known to the ancients as *morbilli,* the diminutive of *morbus,* meaning "little disease," to distinguish it from smallpox, regarded as the "great sickness." Later, it was spoken of as rubeola, derived from the Arabic, meaning "red spots." Regarded as one of the most highly communicable acute human diseases, measles is caused by a specific virus, designated by some workers as *Briareus morbillorum.* It occurs most frequently among pre-school and young school children. However, it readily attacks adults in populations not previously exposed or heightened virulence of outbreaks may occur among groups in which are found an appreciable number of susceptible individuals. Measles is a world-wide problem.

Although measles *per se* is seldom fatal, serious complications and secondary infections occur frequently. The virus of measles produces alterations in the mucous membrances of the upper respiratory tract and in the pulmonary tissues. The morbid process, thus initiated, lowers resistance and the altered tissues become more susceptible to invasion by potentially pathogenic microorganisms already present or which are acquired during the course of the disease. The incidence of secondary complications is between 15 and 20 per cent. Most common are infections of the sinuses, the middle ear, and the pneumonias—complications usually controlled by antibiotics and other antibacterial therapeutic agents. Post-infectious encephalitis, though infrequent, is the most serious complication which may occur. Approximately one-third of those developing encephalitis either die or exhibit permanent neurological residuals. Measles also affects deleteriously pre-existing chronic abnormalities, such as cystic fibrosis, tuberculosis, etc.

Various products have been used to prevent measles. In the treatise by Home (1759) and in other literature of the eighteenth and nineteenth century are accounts of human inoculations with blood and other materials, such as secretions from the upper respiratory

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tract, obtained from patients having measles. This so-called "morbillisation" was similar to the variolation or procedure of inoculation first practiced as a prophylactic measure against smallpox. More recently, the use of convalescent serums, placental extracts, and especially gamma globulin has been and still is employed after exposure as a prophylactic by passive immunization. Attempts to prepare an attenuated or inactivated measles-virus vaccine and employ this as an active immunizing agent were made almost four decades ago. Its effectiveness was not clearly demonstrated. However, not until the past few years was there available a practical method for active immunization with a living attenuated virus or an inactivated virus in which the protection offered was clearly demonstrated by a high index of serologic response and the absence of untoward reactions.

A. *The History of Measles Immunization With Attenuated Virus*

In 1939, Rake, Schaffer and Stokes (1, 2) reported that they had attenuated measles virus by passage in the chick embryo. However, passage of this virus to monkeys for viral assay gave unreliable results because of a high percentage of immune monkeys in their experimental group. Furthermore, clinical studies indicated that children inoculated with the attenuated vaccine were not protected against the natural disease. Arakawa (3), a Japanese worker, reported (1948-49, 1956) that his group passed the virus in mice and later to eggs and had developed a "fixed" measles virus. Taniguchi (4) in 1956 inoculated humans intranasally with an egg-passed measles vaccine. He reported that it successfully prevented severe measles infection.

The Russians developed an attenuated vaccine in human lung tissue. When inoculated into human subjects, this vaccine caused fever in 1.2 per cent of the subjects, exanthema in 1.9 per cent, and antibodies in 50 per cent. However, no protection was conferred against virulent measles in the test subjects (5). Several large research teams in Russia have continued working on the production of a measles vaccine, especially at the Institute of Virology at the Academy of Medical Sciences of the U. S. S. R. More recently, Lebedev and associates (6) tested three vaccines with encouraging results, and Smorodintsev and his coworkers (7) reported similar findings with a live tissue culture vaccine.

B. *The Work of Enders and Peebles*

In 1954, Enders and Peebles (8) isolated measles virus in human and monkey kidney cultures from throat washings and samples of blood collected from measles patients. These specimens were collected within 24 hours of the appearance of the rash. The cytopathogenic changes observed in the tissues affected by the virus have been described (9). These cellular changes were suppressed by antisera from convalescent measles patients but not by their acute phase sera. The virus was maintained through ten serial passages and continually produced measles complement-fixing (CF) antigen. The work of Enders and Peebles was subsequently confirmed by other workers, using both normal and malignant tissue culture cells.

C. *Measles Antibody Studies in Monkeys*

Peebles *et al.* reported in 1957 (10) that monkeys held in captivity for various periods developed measles antibody, whereas animals tested immediately after capture or kept in strict isolation had no antibodies. Therefore, when the tissue culture propagated measles virus was passed to these immune monkeys, no infection or symptoms were observed. This immune state in primates probably accounts for the confused results obtained by Rake *et al.* (2) in 1941.

When non-immune monkeys are experimentally infected with tissue culture-passed virulent measles virus, the following findings are observed:

1. Viremia between the fifth and twelfth day,
2. Leucopenia,
3. Rash between the ninth and twelfth day in 50 per cent of the animals, and
4. CF and neutralizing antibodies, which are equivalent to or higher than titers seen in human measles infection.

Since Enders and his coworkers felt that these results were reliable and reproducible, preliminary studies were undertaken to produce a tissue culture attenuated measles vaccine.

D. *The Method of Attenuation*

1. It was decided to develop the vaccine in the chick embryo, since this host system eliminates the latent virus problem associated with monkey kidney tissue.

2. In 1957, Mikovanovic and Enders (11) adapted the "Edmonston" (isolated from a patient by that name) strain of measles virus into the chick embryo amniotic sac after passage in human amniotic tissue cultures. The results could not be repeated with five other strains of measles virus. The virus had no adverse effect on the developing embryo and few abnormalities were observed in the newly hatched chicks.

3. Although the virus multiplied abundantly in the embryonated egg, Enders decided to adapt it to chick tissue culture to reduce the amount of chick and egg protein that would be present in the vaccine (12). He chose a virus passage that had undergone 24 human kidney, 28 human amnion, and 6 embryonated egg transfers. No cytopathogenic changes or virus multiplications were observed until the fourth chick tissue culture passage, when spindle and stellate cell formations developed in the infected culture tubes (12).

4. An aliquot of the fourteenth chick embryo tissue culture measles passage was inoculated into cynomologous monkeys, so as to determine if any decrease in virulence had developed. Various routes of inoculation, such as intracerebral, subcutaneous, intravenous, and intrasternal, were utilized (12). Regardless of the route of inoculation, no signs of the disease developed. A slight leucopenia was noted between the 7th to 11th day post inoculation. Virus was isolated (on the 17th day) from the blood of only one of twenty-six monkeys tested and exanthema was not observed on any of the test animals. CF and neutralizing antibodies developed between 15 to 19 days, and their titers were equivalent to those seen in natural infection. These antibodies have persisted for at least two years. Avirulent virus vaccine test monkeys were found to be resistant to virulent measles virus challenge by the intranasal and intravenous routes of inoculation; however, the virulent virus was able to establish itself in the nasopharynx area for at least two weeks. Virus could not be isolated from the blood and spinal fluid of monkeys receiving the live vaccine intracerebrally and intrasternally, but it was present in these

areas when these were sites of inoculation with challenge virus. The animals were later sacrificed and their spinal cords sectioned and stained for pathological studies. No pathology related to measles was observed in any of the test animals. Intranasal inoculation of monkeys with the avirulent vaccine produced neither antibodies nor viremia.

E. *Preparation of the Vaccine*

1. The twelfth chick tissue culture measles passage in enriched media was used as the stock vaccine seed pool. The thirteenth passage was also kept for seed vaccine, and the fourteenth passage was used for vaccine inoculation and designated as Vaccine "A". Roux bottles were seeded with chick fibroblast cells and incubated about three days for cell monolayers to develop for virus inoculation. After the monolayers were washed with Hanks salt solution, the seed virus was added and the bottles fed with medium 199. The virus solutions were harvested on the eleventh day post inoculation, centrifuged to remove all debris, and stabilized with 5 per cent albumin. A series of safety tests were conducted to rule out "wild viruses" and contaminating bacteria. No pathology was observed in monkey spinal cord tissues (13).

2. Vaccine "B" (the second lot of prepared vaccine) received six more passages in the chick embryo amniotic cavity. This was followed by four passages in chick fibroblast tissue culture with the thought that these additional passages would further attenuate the virus.

3. The attenuation process produced some interesting information about the characteristics of the virulent and attenuated strains of virus. First, the virulent measles virus gives larger and better defined plaques on various cell lines than the attenuated virus. Second, the virulent strain causes more rapid cytopathogenic effects and higher virus yields not only in chick fibroblasts cells but also in Hela and human amnion cells. Enders speculates that the lower CPE and lower virus titers associated with the attenuated virus may be due to the formation of interferon, and the mode of action of an attenuated measles vaccine in the body may actually be due to the stimulation of interferon in the body. The attenuated strain produces two to four times as much interferon on the virulent measles virus (12, 14).

Preliminary Clinical Studies Utilizing the Attenuated Measles Vaccine

Katz *et al.* (15) reported that the Vaccine "A" has been tested by himself and three other investigators in a total of 79 children (most of whom were retarded). The vaccine was used on laboratory individuals before the field trials with no adverse reactions. It did not stimulate a booster effect in any of the laboratory workers.

A. *Clinical Results of Vaccine "A" Study*

It was observed that: (1) Eighty per cent of the inoculated children developed a fever of 100°F. or higher from the vaccine. The average temperature of the fever group was 102.2°F., with one individual having 105°F. However, the fever lasted only three days, as compared to six to ten days for the natural disease. (2) Fifty-two per cent developed a rash of two to three days duration, as compared to four days or greater with the natural disease. The rash generally appeared on the tenth to eleventh day, and seemed to be reduced in intensity. (3) Koplik spots appeared in 22 per cent of the vaccinated children as compared to 95 per cent with the natural disease.

B. *Route and Size of Vaccine Inoculum*

1. Katz, Enders and Halloway (16) employed 0.1 ml. subcutaneously or intradermally. Nine children, who received the vaccine, developed antibodies regardless of the route of inoculation. The number of virus particles (TC ID_{50}) was not given.

2. Black (17) inoculated 0.15 ml. subcutaneously into nine children. All the subjects developed antibodies. He believes he injected about 50 virus particles per dose.

3. Kempe (18) used both the intradermal and subcutaneous routes interchanging 0.1 ml. and 0.05 ml. doses. Twenty-two of 24 children developed antibodies. The two children who failed to respond to the antigen received 0.05 ml. intradermally.

C. *Excretion of Virus and Its Effects on Contacts*

The above investigators reported that virus could not be isolated from either the throat or the blood of the experimental subjects. Virus could not be isolated from contacts of these children.

D. *Antibody Levels*

Most antibody rises by the complement-fixation test were from 1:32 to 1:128. This is the level which generally develops from the natural disease.

It was noted that: (1) Catarrhal symptoms were reduced in the immunized groups as compared to the natural disease. (2) The duration of the disease was shortened. (3) No central nervous symptoms had developed. (4) The vaccine was noncommunicable. (5) The vaccine was not disabling to the children. Although rash and fever developed, no decrease in their normal activity was observed. However, it appeared at this stage that an inoculation of measles vaccine "A" acts more like a modified disease than a truly attenuated measles vaccine.

E. *Studies on Measles Vaccine "B"*

This "B" vaccine was administered to about 50 children (13). However, it developed that only seven children in this group were susceptible. They all gave antibody rises to measles virus. There were no exanthema, but three had fever.

F. *Laboratory and Clinical Studies by Black (Yale Medical School)*

Black (19) studied the protective effect of natural measles antibodies in institutionalized children against an epidemic of measles. He found that individuals with pre-infection titers greater than 1:8 did not develop the disease and that children with a titer of $<1:4$ did develop measles. One of six children with a titer of 1:4 and one of eight children with 1:8 had a clinical disease.

Ninety-two per cent or twelve of thirteen children with neutralization titers of $<1:2$ had clinical measles. Individuals with titers of 1:2 to greater than 1:8 did not get the disease. Therefore, Black noted that one requires serum neutralization and complement-fixation titers of about 1:8 for solid immunity. However, the interpretation of the results of these tests is often not too reliable with serum dilutions of less than 1:8.

In Black's studies, the four routes of inoculation utilized were the subcutaneous, intranasal, oral, and conjunctival. The latter three were chosen inasmuch as they were more closely related to the natural route of measles infection and might yield a more efficient method of vaccination with minimal clinical illness.

1. *Subcutaneous Inoculation*

Nine children received 0.15 ml. of live vaccine which contained about 50 virus particles (1.5 ID_{50}). All the children developed antibody rises, which were between 1:16 and 1:256 by both complement-fixation and serum neutralization tests. The two serological techniques apparently gave almost complete correlation with measles in his hands. Seven of nine children became ill, the disease appearing similar to gamma globulin modified measles. Three children had extensive rashes; one, a moderate rash; and three, a mild rash. Most of the children had fever, which ranged from 102° to 105°F. The white blood cell count was lowest about the 7th day. Lymphocytes first decreased then increased with the appearance of the rash, while neutrophiles decreased at this time. Band cells also tended to rise in number with the appearance of rash and fever. The sicker the child became, the higher were the titers of the CF and SNT antibodies.

2. *Oral Inoculation*

Ten children had the top and bottom of the tongue and back of the mouth swabbed with the vaccine. This method of inoculation proved to be totally ineffective. No antibody rises were observed and none of the children became ill.

3. *Intranasal Inoculation*

Five children had the nasal area swabbed with a gentle rolling motion, so that little trauma or abrasion occurred. Approximately 3000 virus particles were contained in 0.1 ml. of virus inoculum. Three of five children developed CF antibodies for measles, and a fourth child had a low borderline titer (1:4). The titers were somewhat less than the subcutaneous titers, but all showed at least a 4-fold rise over the first serum. Three children developed rashes and two developed fever by the intranasal route. The incubation period was 8 to 10 days, as compared to 7 days for the subcutaneous inoculation.

4. *Conjunctival Inoculation*

Five children were inoculated by this route with rather unreliable results. It was observed that no local eye reactions occurred with the vaccine. Febrile responses could not be accurately deter-

mined because of respiratory illness present in the institution at the same time as the experimental study. However, one child did develop a rash, but there was no increase in measles antibody; a second child developed antibodies but no rash or fever. Cough or coryza was not observed in any of the children, regardless of the route of inoculation of the vaccine.

G *Additional Clinical Trials of a Measles Vaccine*

Stokes *et al.* (20) inoculated subcutaneously thirteen infants, four to thirteen and a half months of age, with 0.25 ml. of Ender's live attenuated measles-virus vaccine B. Five infants, who were seven months of age or older, were devoid of detectable measles neutralizing or complement-fixing antibody in their prevaccination serum sample, and all eight infants, who were six months of age or younger, showed the presence of detectable measles antibody. All the five older infants, who were initially devoid of antibody, became infected after vaccination, as indicated by the development of a measles neutralizing and complement-fixing antibody response. In four of these five infants, a febrile disease developed. In two of these four, the illness was typical of modified measles. None of the eight, who had neutralizing antibody initially, showed an increase in antibody titer, suggesting a lack of superinfection. They indicate that the mild illness which accompanies the vaccination "is certainly to be preferred" to the natural disease, "providing that the immunity is lifelong or, if not, that waning immunity can be effectively reinforced." They also suggest that a killed virus vaccine for reimmunization is probably "more applicable when an antibody is present."

Krugman and associates (21) administered live measles vaccine to 23 of 46 children with negative measles complement-fixation tests. Febrile reactions of varying degree were observed in about 90 per cent of susceptible patients. A rash occurred in 61 per cent. Respiratory symptoms were absent or minimal. Fever or rash were the only untoward effects. The 23 unvaccinated controls gave no evidence of contact infection as a result of exposure to the immunized group. A significant rise in measles complement-fixing antibody was detected in eighteen of twenty-three children, twenty-one days after vaccination. The five nonreactors were considered probably immune before vaccination. An epidemic of measles occurred in the building seven weeks after the vaccine was administered. All twenty-three

vaccinated patients were solidly protected. The attack rate in twenty-three unvaccinated controls was 74 per cent (19).

The Lederle group (22) reported some early immunization experiments with the live measles vaccine. Using 6000 TC ID_{50} of virus as the immunizing dose, they obtained an antibody response with the symptoms of modified measles. They were able to evoke an antibody response in two children with as little as 6 TC ID_{50}. In other experiments, they inoculated virus concentrations as large as 6000 TC ID_{50} in post-measles patients without reinforcing their antibody level.

H. *Other Measles Vaccines—Combined Therapy*

Studies with the attenuated measles-virus vaccine derived from the avianized Edmonston strain are reported above. A chick-cell-culture adapted live measles-virus vaccine is described by Smorodinstev and associates (7). Children in the Soviet Union inoculated with the latter elicited a high immunity response and very little clinical reactions.

McCrumb and associates (23) of the University of Maryland School of Medicine reported on the use of a live measles-virus vaccine, the virus having been adapted to canine renal cell culture. The antibody response "appears to be comparable to that which follows natural immunity." The vaccine was administered by a parenteral route (intradermally and intramuscularly) and by a respiratory route (intranasal, aerosol, and conjunctival). "Immune response was not influenced by the method of administration of the virus." The workers in this group (24) conducted further studies in an attempt to evaluate an attenuated live measles vaccine prepared from canine renal cell culture and one (Edmonston strain) prepared from chick embryo cell culture, when administered by various routes. They noted that the human host is more sensitive to the latter type of measles vaccine than to that of the canine renal cell culture system. They also concluded "that vaccination by a respiratory route has the disadvantages of high reaction rate and, in the case of intranasal immunization, unpredictable take-rates." In an effort to reduce reactions in susceptible children, the latter were given pooled human gamma globulin one week after the intramuscular inoculation of canine kidney cell measles vaccine. They noted that this combined immunization procedure gave "a marked modification of clinically

overt reaction." On the basis of the latter finding, this same group of workers proceeded to develop "a practical method of large-scale immunization." They reported first on 158 susceptible school children in St. Joseph, Mo. Of the latter group, "143 children (91%) were successfully immunized by this method without an appreciable number of clinically significant reactions." They indicate that the measles vaccines by themselves "are not suitable for community use" and that a combined immunization procedure employing gamma globulin and attenuated vaccine would appear to be the only practical method for large-scale immunization against measles presently available. The simultaneous intramuscular injection of gamma globulin with vaccine was not associated "with impairment of immunogenicity" (25). Hundreds of children are being tested in Baltimore by this method and they expect to have "6000 tests ready to report at the international conference of measles immunization to be held at the N. I. H., Nov. 7-9, 1961" (26).

Stokes *et al.* (37) report on "a controlled study to evaluate the efficacy of the Enders vaccine administered immediately before an attenuating dose of human immune globulin. The findings are presented in terms not only of serologic response to vaccination but also of the prevention of natural measles in epidemics." The live-virus vaccine was prepared from a seed virus, which "had been passed twenty-four times in primary cell cultures of human kidney, twenty-eight times in primary human-amnion cell cultures, twelve times in embryonated hen's eggs and nineteen times in cell cultures of chick embryo." A killed-virus vaccine was also employed as a control. The latter was prepared from a "strain of measles virus grown in renal-cell cultures of the grivet monkey" and "inactivated by treatment at 37°C. with 1:4000 formalin." The 605 children involved including the controls (those injected with the killed-measles virus vaccine) were later exposed to natural measles. "The live-virus vaccine administered with human immune globulin proved 100 per cent effective in preventing natural measles on intimate exposure."

I. *The Close Relationship between Measles and Canine Distemper Virus*

Canine distemper and measles viruses produce similar clinical syndromes and histopathologic changes in their respective hosts. Skaggs (27) discusses the antigenic relationship between the two.

Adams and Imagawa (28) reported a close relationship of canine distemper virus to measles virus. The cytopathic effect of measles virus in tissue culture was neutralized by canine distemper antiserum. Using suckling mice, they reported neutralization of canine distemper virus by measles antiserum. Ferrets immunized with measles virus were partially protected against distemper. These observations were not confirmed by Katz, who failed to detect measles complement-fixing and neutralizing antibodies on canine distemper serum. Cabasso (29) also noted that there was no antigenic relationship between measles and distemper viruses. Schwarz and associates (30) reported both a poor antigenic and a poor protective effect against measles in their studies of distemper vaccine. The distemper virus lacked the antigenic component, which might cause significant measles antibody production. These workers used a chick embryo tissue culture (CETC) vaccine during a measles epidemic in Panama in 1959. They "concluded that, while the measles vaccine was effective, the high rate of reactions limits its usefulness." Gillespie and Karzon (31), in a recent study, noted that "all measles-inoculated dogs, including those with no demonstrable canine distemper neutralizing antibody, were protected against intravenous or intracerebral challenge with virulent canine distemper virus, while the contact controls, not receiving measles virus, became ill, and some died."

Riazantseva, N. Ye *et al.* (38) of the Measles Laboratory, U. S. S. R. Academy of Medical Sciences in Moscow, present a "study of the immunological affinity of measles and canine distemper viruses." They detail a description of four experimental series and conclude that "Experiments on puppies failed to reveal an immunological affinity between canine distemper and measles viruses. Nor was there complete similarity in the pathological changes induced by these viruses in the experiments on dogs."

J. *Studies on Measles Virus*

As more information is made available concerning the virus of measles, it is apparent that a more effective measles vaccine will be possible. Among the numerous recent studies on measles virus are those on its growth and stability by Black (32), the physical properties and various inactivation findings by Musser and Underwood (33), the antigenicity of live and killed measles virus by Dewitt and

Nook (34), and further studies on the use of a mouse-fixed measles virus for the preparation of a vaccine by Arakawa and associates (35).

Rozental and Kopytovskaia (39), of the Institute of Experimental Medicine, U. S. S. R. Academy of Medical Sciences, Moscow, outline experiments on the isolation of measles virus by direct infection of fertile eggs with the blood of patients. They (1) "demonstrated by the method of antigenic curves" that transfer from the infected chick embryos to explants of kidney epithelium caused "changes characteristic of measles virus with formation of typical intranuclear inclusions." (2) "The egg and tissue lines of measles virus did not differ antigenically;" and (3) "Confirmation was provided for the statement that measles infection in chick embryos is asymptomatic and also the suitability of the method of antigenic curves in detecting virus in these conditions was established."

Conclusions

At this time, it seems appropriate to recommend extension of clinical trials of attenuated live measles-virus vaccine in special groups and a conservative extension of its use in normal children (15). Acceptance will depend on an awareness by everyone of the hazards attending natural measles and a recognition of the fact that reactions may occur when using the vaccine. Laboratory efforts are continuing in an attempt to provide a preparation that may induce comparable serologic response and immunity comparable to natural measles, with less febrile and other untoward reactions.

In an editorial by Riley (36), the final summation is to be noted: "While additional refinements are needed before the vaccine can be used as a routine measure, it would appear that a safe and effective prophylaxis against measles is near. However, before the ultimate benefits from vaccination can be realized, it is necessary that the public be educated to a realization of the great hazards of measles and to acceptance of the vaccine."

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THE SYSTEMIC ABSORPTION OF AN ORALLY ADMINISTERED PROTEOLYTIC ENZYME, BROMELAIN

By R. D. Smyth, R. M. Brennan, and Gustav J. Martin *

Introduction

WHEN orally administered proteolytic enzymes were first offered to clinicians, the question most frequently asked was "How do you know the enzyme is absorbed?" The answer to this question takes two forms. The first relates to the fact that it makes no difference whether the enzyme is or is not absorbed; the issue is whether or not a clinical effect is manifested. To the question of clinical effectiveness, a large number of clinicians have offered evidence (1). This is the key. An orally administered enzyme might cause the production of secondary enzymes or biochemicals which would be absorbed and cause the effects observed. The second relates to actual demonstration of absorption.

Evidence for the absorption of orally administered enzymes in animals has been obtained by the use of I-131 tagged materials (2). Clinically, the work of Miller and his associates (3-4) demonstrated the absorption of I-131 trypsin. Similar results were recently reported for chymotrypsin (5). Miller emphasized that his observations relate to a protein-bound iodine demonstrated in the blood stream following the oral administration of trypsin I-131. The rational conclusion is that this material is trypsin I-131 but direct proof is not available.

When work was initiated in this laboratory with bromelain, it was deemed advisable to seek a method for the demonstration of the absorption of an orally administered enzyme which would be novel. The use of fluorescent dye-labelled proteins (6) was proposed to us by Dr. Ralph Heinicke of Dole Corporation in Hawaii. He had prepared bromelain labelled with 5-dimethylamino-naphthalene-sulfonyl chloride and found that the enzyme retained 95 per cent of its activity. This seemed the best approach to our problem and the study was undertaken.

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Methods

Two compositions of fluorescent dye conjugated with bromelain were prepared. The first was a liquid preparation and was made by mixing 2 Gm. of bromelain (Dole) into 100 ml. of distilled water containing 60 mg. of $NaHCO_3$ and 100 mg. of Na_2CO_3. 500 mg. of 5-dimethylamino-naphthalene-sulfonyl chloride on Celite was added and the suspension mechanically shaken for 30 minutes. The resultant mixture was centrifuged and the supernate dialyzed against distilled water until the dialyzing medium was free of fluorescence. A solid material was prepared in a somewhat similar manner by precipitating the dye tagged bromelain out of solution by the addition of 95% ethanol. Both the liquid and the solid dye enzyme preparations were found to be stable in acid and alkaline media.

Dosages varying from 10 to 50 mg. per kilo were administered to healthy albino rabbits (total of seven). The liquid preparation was given using a Jutte duodenal tube; the solid capsule form was given by oral administration. Rabbits were fasted 24-36 hours prior to treatment.

Blood samples were taken from the marginal ear vein at 0, ½, 1, 1½, 2, 2½, 3, 4, and 5 hours after treatment. Animals were then sacrificed and the organs removed and analyzed by fluorescence. The organs were homogenized in 0.9% saline and a supernate was isolated by centrifugation.

Results

As with I-131-tagged proteolytic enzymes so with the dye-tagged product, the question may be raised as to whether or not the measurement of I-131 or the measurement of fluorescence actually relates to the tagged enzyme. Determination of the electrophoretic patterns using paper strips in a Reco Model electrophoretic apparatus with subsequent reading in a transmission densitometer gave the patterns shown in Graph I.

The results show clearly that the dye-tagged enzyme appears intact in the serum following oral administration. The patterns for the serum after dye-enzyme administration parallel that of the dye-enzyme alone or the dye-enzyme added to serum. The electrophoretic patterns of serum or of serum to which 5-dimethylamino-naphthalene-sulfonyl chloride was added *in vitro* do not in any degree parallel.

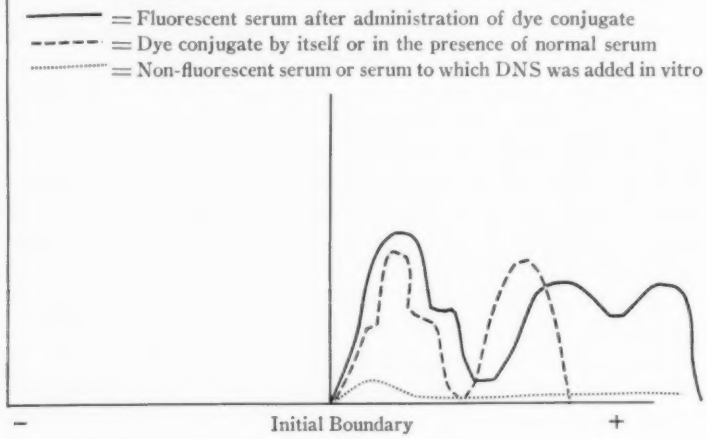
This constitutes qualitative evidence that the dye-tagged enzyme is absorbed and appears in the serum. This observation combined with acid and alkali stability of the conjugate leads rationally to the conclusion that observations relating to fluorescence do in fact reflect the presence of dye-enzyme conjugate.

Direct fluorescence measurements show that the bromelain dye preparation is absorbed from the gastrointestinal tract. When given in the liquid form, blood levels appear in ½ hour and are sustained for 2½ to 3 hours. In the form of the enteric coated capsules, the conjugate appears in the serum in direct relationship to the disintegration rate for the enteric-coated pharmaceutical form. The initial appearance is from 1½ to 2½ hours after dosage and the duration extends from 1½ to 2½ hours after initial appearance.

At the conclusion of the five hour period, examination of the organs revealed that the dye conjugate appeared in the liver, kidneys, and urine but was not present in detectable quantities in the spleen, lung, heart, duodenum, or major arteries and veins.

GRAPH I

PAPER ELECTROPHORETIC PATTERNS OF BROMELAIN FLUORESCENT DYE CONJUGATES PER SE AND IN SERUM



Discussion

As stated in the Introduction, the question of absorption or non-absorption of proteolytic enzymes following oral administration is academic and basic. The enzyme could produce its clinical effect by causing the creation in the intestine of a secondary enzyme or other biochemical which would then be absorbed and result in the alleviation of inflammation and edema as seen clinically. The enzyme could be absorbed and act directly. Finally—and this situation seems to be the most probable—both actions might be basic to an explanation of the clinical utility.

In any event, the results here presented demonstrated the absorption of bromelain-dye conjugate following oral administration. From this, it is rational to conclude that the bromelain itself is absorbed in a similar manner.

The timing of the appearance of the conjugate and its duration of maintenance of blood levels coincides with the timing on initiation of effect in egg white edema. The therapeutic effect of proteolytic enzymes administered orally begins in approximately one hour and extends over a period of two or three hours. The correlation of these time data substantiate the basic conclusions relating to enzyme absorption.

It will be of the greatest importance to determine the rate of appearance of the enzyme properly tagged at the site of an inflammatory reaction with edema. The I-131 work on this point is confusing. Bogner *et al.* (7) reported higher levels of radioactivity in edematous legs as contrasted to control legs of rats following the subcutaneous injection of I-131 trypsin. In contrast, Miller *et al.* (8) noted that trypsin I-131 did not appear at the site of inflammation in as great an amount as at the region of the control. They attribute this to reduced blood supply to the inflammed area. Trypsin I-131 remained at the site of inflammation for a prolonged period of time. Hypothetically, the anti-inflammatory enzyme should concentrate at the site of inflammation although this is not essential to function as small quantities of enzyme may activate plasmin locally and bring about the therapeutic action desired. Future work with dye-tagged bromelain should bring clarification to this problem.

Conclusions

Conjugates of bromelain with 5-dimethylamino-naphthalene-sulfonyl chloride were prepared and administered to rabbits in doses varying from 10-50 mg. per kilo. Absorption occurred which could be detected ½ hour after administration of the conjugate in a liquid form and after 1½ to 2 hours when given in solid form as an enteric-coated capsule. At the conclusion of a five hour period, the animals were sacrificed and fluorescence was observed in the liver, kidney, and urine but not in the spleen, lung, heart, duodenum, or major blood vessels.

The correlation of these observations with clinical findings is discussed.

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MANAGEMENT OF HODGKIN'S DISEASE AND THE LEUKEMIAS WITH CYTOXAN

By John R. Sampey *

CYTOXAN is one of the most promising of the new drugs in the management of malignant blood diseases. Within the span of three years from its synthesis, it has undergone clinical trials with more than five hundred patients with Hodgkin's disease and the leukemias. Cytoxan is a cyclophosphamide nitrogen mustard, N,N-bis(beta-chloroethyl)-N',O-propylendiamide ester of phosphoric acid, which goes under the names also of endoxan, cyclophosphamide, and B 518. In this study, an attempt is made to give a preliminary evaluation of the drug in the control of Hodgkin's disease, acute leukemia, chronic lymphocytic leukemia, and chronic granulocytic leukemia.

Hodgkin's Disease

Cytoxan has been administered to several hundred patients with Hodgkin's disease, and the results are set forth in more than two dozen published reports covered by this review. Gerhartz and associates (13) reported 30 good and six partial remissions lasting as long as seven months in 37 patients. Eckhardt *et al.* (10) described 17 remissions in 28 patients with two lasting over 12 months, with six extending over six months, and nine ranging from one to six months. A year later (11), he noted nine out of 15 patients improved who were placed on cytoxan therapy; this compared with 16 remissions in 28 patients administered degranol, with 10 of 13 receiving HN2, and with three of eight given nitramin therapy. Bethell *et al.* (3) observed objective improvement in seven of 26 patients which lasted from 30 to 219 days, but the toxicity of cytoxan was so severe in 11 patients that the treatments were discontinued. Matthias *et al.* (24) recorded 11 objective responses and 15 subjective improvements in 17 patients and, in contrast to the preceding report, they commented on how well the drug was tolerated. Truhaut *et al.* (36) reported eight objective but partial regressions in 14 patients, which lasted to 11 months. Kuenboeck *et al.* (23) treated 15 patients with endoxan, and observed eight remissions, which extended to 26

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months; the average duration of remissions was 13 months. Korst *et al.* (22) noted seven satisfactory remissions in 12 patients, with one complete remission for eight months. DiPietro (7) described nine good and one partial symptomatic response in 11 patients, and three good and eight partial regressions in tumor size in the group. Gross has released three clinical reports on the use of cytoxan in the management of Hodgkin's disease: in one, he and Lambers (14) noted four partial responses in four patients and, in a second report (15), they judged fair improvement in three of four cases. Later, Gross (16) described one complete, five extensive, and three slight remissions after use of cyclophosphamide in 10 patients. Coronho and Alpert (5) stated that five of six patients had objective responses, and Shnider *et al.* (33) noted three objective remissions in six cases. Bergsagel and Levin (2) recorded three partial remissions in six patients. Santoro *et al.* (31) noted some clinical improvement, together with a decrease in tumor size in four patients after endoxan therapy. Cramblett (6) induced complete remissions in two of three patients, which lasted for three and four and a half months, while Saitmacher (27) obtained some improvement in two of three patients, but the third was made worse by cytoxan therapy. Papac *et al.* (25) reported partial remissions in three patients. Good objective responses were noted in two patients by both Haar *et al.* (17) and Hammer and Enderlein (18), while Aronovitch *et al.* (1) secured objective improvement in one of two patients. Schwenkenbecher (32) described a patient who did well for two years on endoxan, and Terazawa *et al.* (35) noted regression of tumors in one patient. Dubois-Ferriere *et al.* (8) employed the combination of cytoxan plus prednisone to induce a good clinical remission in a patient, and he and Kalaci (9) administered endoxan plus large doses of prednisone plus x-rays to secure good palliation in another patient. Host and Nissen-Meyer (21) administered 17 treatments of cytoxan, and reported 10 good responses and two which were moderate; they concluded that this N-mustard was better than HN2, because of less marked bone marrow depression.

Acute Leukemia

Hoogstraten released two studies in 1960 on a comparison of daily versus weekly doses of cytoxan in the control of acute leukemia: in one (19), he recorded three partial and one complete remission in

32 patients on a weekly dose schedule, and he noted one partial and two complete responses on daily doses, but steroids influenced two of the latter remissions. In a second report, he and associates (20) tabulated one improvement in 11 patients who were under 20 years of age, and who received daily doses of endoxan; in 26 patients under 20 years on weekly doses, they recorded two complete remissions, two partial, and eight who showed improvement; in 25 patients over 20 years who received daily doses, they found two partial remissions and one who was improved; finally, in 20 patients above 20 years who were on a weekly schedule of the drug, they recorded three partial remissions and three improvements; no significant increase in survival was noted in any groups. Fernbach *et al.* (12) achieved complete remissions in four of 18 children who were given cytoxan, and they concluded that the drug possessed significant clinical value. Bethell *et al.* (3) noted three complete remissions of 14 to 216 days, and three partial ones in 14 patients. Spurr and Hayes (34) noted three complete remissions to 28 days and two partial remissions to three weeks in seven patients with acute lymphocytic leukemia, but they observed no response in two cases of acute myelocytic leukemia. Gerhartz *et al.* (13) evaluated only three of six patients: there was one good and two partial remissions for 0.6 month. Cramblett (6) secured remissions of one and three months in one patient with acute lymphoid leukemia and in one with acute myeloid leukemia. Papac *et al.* (25) found a partial remission in one patient after treatment with endoxan, but Coggins *et al.* (4) noted no effect in another case. Dubois-Ferriere *et al.* (8) used the combination 6-mercaptopurine plus endoxan to induce a good hematologic response in a child.

Chronic Lymphocitic Leukemia

Bethell and eight associates (3) described eight objective improvements in 19 patients with chronic lymphocytic leukemia who had cytoxan administered; the remissions were noted for 287 days and were in effect at the time of reporting. Gerhartz *et al.* (13) chronicled five good and one partial response in seven patients, which lasted to 2.1 months. Haar *et al.* (17) described marked decrease in the white blood cells in five of six patients but only slight clinical improvement. Matthias *et al.* (24) secured three objective and three subjective improvements in five patients, while Shnider *et al.* (33) observed only one objective response in five others. Eckhardt *et al.*

(10) tabulated one remission lasting over 12 months, and three for six months in four patients. Truhaut *et al.* (36) reported that two out of four patients had partial remissions to nine months. Höst and Nissen-Meyer (21) described one patient who had a moderate response to both HN2 and endoxan. Gross (16) noted extensive remissions in two patients. In an investigation of combination chemotherapy, Dubois-Ferriere and Kalaci (9) recorded a two year remission in a patient following chlorambucil therapy and then, when prednisone and endoxan was administered, there followed a complete remission for six months. This same investigator (8) reported another complete remission in a patient with chronic lymphocytic leukemia who received the combination prednisone plus endoxan.

Chronic Granulocytic Leukemia

Gross conducted three clinical studies on the control of chronic granulocytic leukemia with cytoxan: in one, he and Lambers (14) observed remission in all seven patients tested and, in a second trial, they (15) recorded three fair responses in seven patients; two years later (16), Gross induced extensive remissions in three of nine patients, with the remaining six showing some improvement. Haar *et al.* (17) caused partial remissions in all four patients who received endoxan, and they expressed pleasure at the prolonged responses achieved. Gerhartz *et al.* (13) tabulated four good and one partial remission for 0.6 month in six patients. Bergsagel and Levin (2) failed to note any benefit in two patients, while Coronho and Alpert (5), and Spurr and Hayes (34) both described objective remissions in single cases. Rundles *et al.* (26) observed results similar to that achieved with other N-mustards in their treatment with chronic leukemias.

Discussion

The results from these preliminary trials of the N-mustard, cytoxan, in the control of four blood diseases are summarized in Table I.

These data are too limited to permit any general conclusions, but they do suggest some interesting comparisons with the results achieved with the older nitrogen mustards during the past decade: (1) The remission rate of 70 per cent for cytoxan therapy of Hodgkin's disease is higher than the 63 per cent in 4246 patients treated with all

TABLE I

CYTOXAN THERAPY OF HODGKIN'S DISEASE AND LEUKEMIA

	No. of Cases	*Good Remissions*	*Fair Remissions*	*Remission Rate*
Hodgkin's Disease	234	44	121	70%
Acute Leukemia	203	17	35	25%
Chronic Lymphocytic Leukemia	55	10	24	62%
Chronic Myelocytic Leukemia	37	7	23	81%

N-mustards (28), but the ratio of good to fair remissions is much lower; (2) The remission rate of 25 per cent in acute leukemia is 10 per cent below that for 373 patients treated since 1949 (29) with older N-mustards, and the proportion of good to fair responses is approximately the same; (3) The 62 per cent rate for cytoxan in chronic lymphoid leukemia is significantly lower than the 77 per cent found in 762 patients previously (30), and the proportion of good remissions is disappointing for, with the older N-mustards, the number of good surpassed the number of fair remissions; (4) The few results in chronic granulocytic leukemia indicate about the same remission rate with cytoxan as that noted in 673 patients on other N-mustards (30) and, for the third time in this study, the proportion of good to fair responses is disappointing. The criteria, however, for assigning "good" and "fair" remissions vary widely with different investigators, and there is a growing disposition of clinicians to reserve the term, good, for those cases which show complete remissions, or the absence of clinical and/or hematologic signs of the disease.

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CONGESTIVE FAILURE

By Tom Langford, Jr.* and William B. Swafford **

ONE of the worst maladies existing in the independently owned pharmacy of today is congestive failure. The prescription department has long been recognized as the heart of the independent pharmacy and its importance to the success of the pharmacy can be likened to the physiological significance of the human heart to man.

Does it seem reasonable to allow so important a department to atrophy and gradually slough to the extent that returns are not up to expectations? That is exactly what is happening and will continue to happen unless owners awaken to the danger and provide ample therapy.

The independently owned drug store has lost a tremendous majority of its sundry business to non-professional outlets. What is being done toward this problem? Strategy of large scale merchandising, gaudy displays, and special cut-rate sales. In effect, we are crowding out our all important prescription department. We are congesting our prescription department with a maze of sundry items ranging from shower-clogs to motor oil. This is certainly not professional pharmacy as one would attempt to sell the public and the government as well. This is nothing more than a merchant with a department containing prescription merchandise.

The human heart when confronted with congestion compensates by hypertrophy and not by atrophy as our prescription departments are doing. We suggest getting rid of the departments that are not pharmacy, that are not related to the healing arts, that are not necessary for the high standards of community health. We realize that it is each man's prerogative to decide what his store will or will not contain. We are only presenting a point which must be considered if we are to have the independently owned pharmacy, if we are to establish pharmacy as a profession, if we are to realize a fair monetary return.

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There are many items which can be ancillary to the prescription department without congesting this vital organ of pharmacy. Surgical supplies are very important to the health of the community and the drug store can and should be the nucleus for retail distribution. Hearing aids could be added by training one or two sales clerks or a pharmacist to handle the technicalities. Dietary foods for the obese or diabetic would look much more appropriate in a drug store as compared to a rack of toys or greeting cards. There are many more additions and subtractions that could be made to establish the corner pharmacy as a center for medicines, health needs, hospital and surgical supplies. Is there any pharmacist, concerned about his professional stature and future, who is pleased to own and operate a "glorified variety store?" It is our opinion that there are very few.

There are many pharmacists who run at the mention of the word, "apothecary." They associate this with an establishment consisting only of a prescription department. We are not advocating a movement to apothecaries but a movement to pharmacy. The cluttered pseudo-pharmacies that are cutting off the life lines of the prescription department must be revamped and reconstructed to once more open to the disillusioned public a scene of a professional and health-contributing establishment. It is high time we get more from the public than thoughts of being a merchant with a "high-priced" department. It is time we firmly establish ourselves as professional men and women operating a professional establishment—selling medicines, remedies, and items associated with the healing arts. Relieve the congestion and allow the heart of the retail pharmacy to pump resoundingly. Allow the pulsations to entone the crisp sounds of professionalism instead of the clanging noise of "high prices" and "variety-store hucksters." Allow pharmacy to be presented to the public as pharmacy should be presented and professionalism will be realized as professionalism should be realized.

BOOK NOTICES

Passport to Paradise—? By Bernard Finch. 191 pp. Philosophical Library, Inc., 15 East 40th Street, New York 16, New York, 1960. Price: $6.00.

This book is an account of some common, naturally-occurring drug substances and certain allied products erroneously considered to be a short cut to happiness.

The laudable object in this book has been attempted of familiarizing the reader with certain drugs, some of which are naturally occurring and used in medicine and others which are now very rarely employed, if at all. Used properly, and under medical supervision, potent modern remedies can relieve much suffering and add to the total of human happiness, but misuse can be harmful.

This book covers sedative-hypnotic drugs, narcotic drugs, naturally-occurring local anesthetics, alcohol, old aphrodisiac drugs and other addicting drugs. Their histories of use in human beings and the sources of the drugs are given.

Report of the Central Drugs Laboratory (from 1st April, 1957 to 31st March, 1958). By Dr. H. K. Banerjee, Director. 53 pp. Printed by The Government of India Press, Calcutta, India, 1960.

This report is mainly concerned with the various activities of its five departments. The five departments are (1) Pharmaceutical Chemistry Section, (2) Biochemistry Section, (3) Pharmacology Section, (4) Bacteriology Section, and (5) Pharmacognosy Section.

The report gives a brief and yet comprehensive account of analysis for quality and the amount of various ingredients of both domestic and imported drugs as well as various research activities which the five sections have undertaken.

The statement of examination of drugs tested by each department is given in the Appendix at the end of the report.

Problems of Evolution of Physiological Functions. By the Academy of Sciences, USSR. 162 pp. Moscow-Leningrad, 1958. Translated by Mr. S. Shoshan and printed in Jerusalem by S. Monson. Available from the Office of Technical Services, U. S. Dept. of Commerce, Washington 25, D. C. Price: $1.75.

This book was published for the National Science Foundation, U. S. A., and the Department of Health, Education, and Welfare, Washington 25, D. C. by the Israel Program for Scientific Translations in 1960. It describes the physiological functions of muscles, the nervous system, the endocrine system, and the digestive tract, and the importance of their functional evolution and disorders in man and lower animals with extensive experimental data. The development and peculiarities of the manifestations of the motor functions in man are discussed at the end of this book.

New and Nonofficial Drugs, 1961. 849 pp. J. B. Lippincott Company, Philadelphia and Montreal, 1961. Price: $3.00.

This book is an annual publication of the Council on Drugs of the American Medical Association containing descriptions of drugs evaluated on the basis of available laboratory and clinical evidence. Its scope comprises agents proposed for use in or on the human body for the diagnosis, prevention or treatment of disease, whether or not their usefulness has been definitely established. Descriptions are limited to individual drugs that have not been included in U. S. P., N. F., and N. N. D. for a prior cumulative period of 20 years.

Each drug is described in the form of a monograph to provide: the recognized non-proprietary name (generic name) or names, together with the commercial name; chemical or biological identity; actions and uses, including comparisons with related drugs, limitations, side effects, toxicity, contraindications or precautions, dosage and routes of administration; preparations and their available sizes or strength.

Chapters are arranged according to pharmacologic actions or clinical use, and non-proprietary names are arranged alphabetically under each chapter. Structures are given for most of the drugs under each monograph.

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

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